Biosynthesis of Dictamnine

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DICTAMNINE (I) is the simplest of the furoquinoline alkaloids. We have studied its biosynthesis in *Dictamnus albus* (syn. *D. fraxinella alba*). In separate experiments a number of ^{14}C-labelled compounds were administered to intact mature plants by infusion into the stem through a cotton wick.[1] Radioactive dictamnine, which was isolated from the roots of the plants, was degraded to locate the sites of labelling. The degradation sequences shown in the Figure permitted determination of the activity at each of C-2, -3, -4, -10, and -11 of the dictamnine nucleus and at the *O*-methyl group. The relative specific activities (dictamnine = 100) found at these centres in dictamnine samples obtained from the individual feeding experiments are recorded in the Table.

It is evident that methionine supplies the *O*-methyl group. Radioactivity from the carboxyl group of anthranilic acid enters C-4 of dictamnine specifically. It is therefore likely that an intact

anthranilic acid moiety is incorporated into the alkaloid. Tryptophan cannot then be a stage on the route from anthranilic acid to dictamnine, since the its furan nucleus are vestiges of an isoprene unit, corresponding to C-4 and C-5 of mevalonic acid.[5] If this were so, specific incorporation of acetate into

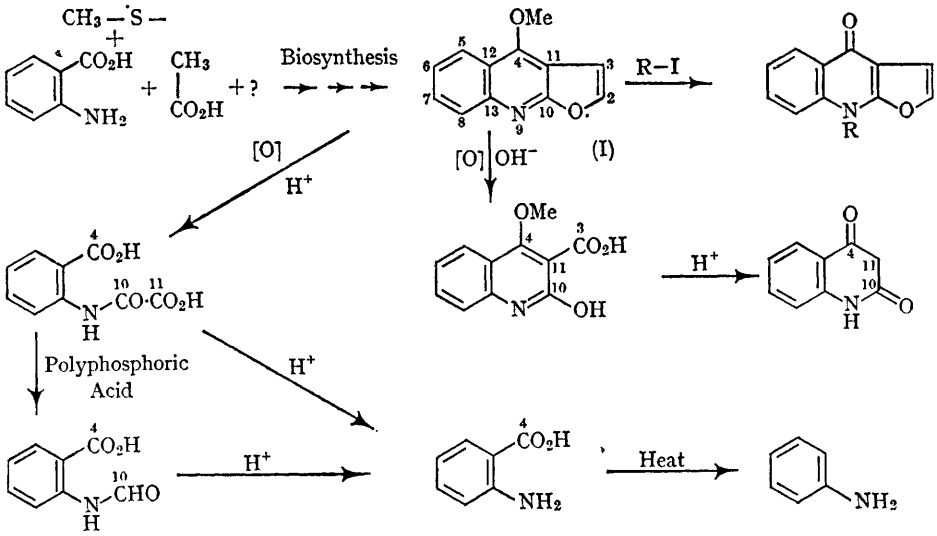

TABLE: *Distribution of radioactivity in dictamnine*

Precursor	Dictamnine Relative Specific Activity (%)* at						
	OCH_3	C-2	C-3	C-10	C-11	C-4	C-5, 6, 7, 8, 12, 13
[Carboxyl-^{14}C]-anthranilic acid	⟵ 0 ± 5† ⟶			⟵ 0 ± 5 ⟶		$\boxed{101 \pm 4}$	0 ± 1
[1-^{14}C]Acetic acid	6 ± 5	⟵ 3 ± 5 ⟶		$\boxed{78 \pm 4}$	3 ± 4	6 ± 1	5 ± 1
[2-^{14}C]Acetic acid	3 ± 4	⟵ 0 ± 4 ⟶		11 ± 2	$\boxed{81 \pm 3}$	2 ± 1	3 ± 1
[Methyl-^{14}C]-methionine	$\boxed{97 \pm 2}$	⟵ 3 ± 1 ⟶					

* Intact dictamnine = 100 + 3.
† Limits shown are standard deviation from the mean.

carboxyl group is lost when anthranilic acid serves as a precursor of tryptophan.[2] The most striking feature of the results is the contrast between the high specificity of incorporation of acetate into C-10 and C-11 of dictamnine and its low level of incorporation[3] into C-2 and C-3.

Furoquinolines are accompanied by alkaloids of the 3-isopentylcarbostyril and the 2-isopropyl-2,3-dihydrofuroquinoline series in a number of rutaceous plants. It has been suggested[4] that dictamnine may be derived from a compound of this type by loss of an isopropyl group, and that C-2 and C-3 of these sites would be mandatory. Even though such specific incorporation of acetate could not be demonstrated, our results leave this possibility open, since it is conceivable that the observed low level of acetate incorporation into the furan carbons merely reflects a low rate of synthesis of mevalonic acid compared to a high rate of entry of acetate into the quinolone nucleus.

Two other hypotheses of the origin of the non-anthranilic fragment of dictamnine, from succinic acid,[6] or from ornithine,[7] are invalidated by the observed incorporation pattern of acetate, as well

as by a lack of incorporation of 5-[^{14}C]-α-oxoglutaric acid. That the quinolone nucleus is not derived from tryptophan, by a route similar to that which gives rise to 4-hydroxyquinoline derivatives in mammals,[2] is indicated by the observation[3] that radioactivity from β-[^{14}C]tryptophan does not enter dictamnine.

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[1] J. R. Gear and I. D. Spenser, *Canad. J. Chem.*, 1963, **41**, 783.
[2] A. Meister, "Biochemistry of the Amino Acids," Academic Press, New York, 2nd edn., 1965, Vol. 2, Chapter VI, N.
[3] The low level of incorporation of label from acetate into C-2 and C-3 of dictamnine precluded individual determination of activity at these two sites.
[4] A. J. Birch and H. Smith, Chem. Soc. Special Publication No. 12, 1958, p. 1.
[5] The specific incorporation, in *Pimpinella magna*, of radioactivity from 4-[^{14}C]mevalonic acid into the α-furan carbon atom of the furocoumarin pimpinellin, has recently been demonstrated (H. G. Floss and U. Mothes, private communication).
[6] H.-G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960", Akademie-Verlag, Berlin, 1961, p. 715.
[7] S. Ghosal, *Science and Culture*, 1964, **30**, 142.
[8] A. O. Plunkett and I. D. Spenser, unpublished results.